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REMARKS/ARGUMENTS

The above-identified application is a continuing application of a national phase application of PCT Application PCT/ES98/00204 claiming priority from Spanish Application Serial No. P 9701816 filed July 31, 1997. The claims for priority and receipt of the certified copies of the priority document(s) were acknowledged in Paper No. 9 (Office Action of August 3, 2001).

Claims 15, 34 and 36 have been cancelled without prejudice. Applicant has replaced claims 34 and 36 with new claims 51 and 52. These claims do not recite the term "comprising". While it is believed the Examiner's interpretation of the term "comprising" in the context of the pending claims is in error, in an effort to advance prosecution, Applicant has so rewritten the claims. This should resolve most, if not all, of the Examiner's concerns and place the claims in condition for allowance.

Further, the new claims 51 and 52 relate to a process wherein the active ingredient of the pharmaceutical preparation is a pyridine methylsulfinyl benzimidazole compound. Representative of this class of compounds (see new claim 53) are omeprazole, lanzoprazole, rabeprazole and pantoprazole and the pharmaceutically acceptable salts thereof. Thus, the previously submitted declaration showings and application examples are adequate in view of the scope of the now pending claims.

Further, the presented claims define the process steps as carried out in a single Wurster type fluidized bed. It is believed that this was clear from the claim language of the previously pending claims.

Claim 15 has been cancelled inasmuch as it was redundant. Claim 25 has been amended to correct a spelling error. New claim 53 which specifically names the active

ingredient has been introduced. This claim is supported by the original application at page 11[1] and the application examples. The other claims have been amended with respect to dependency. The now presented claims do not raise new issues or include new matter. No additional fee is due.

The invention defined by the now pending claims is for a process of producing a pharmaceutical preparation of an active ingredient which is a proton pump inhibitor and of the class of compounds known as substituted benzimidazoles. Such compounds are known to be particularly acid labile and to degrade rapidly when exposed to an acidic environment. See Lovgren's U.S. Patent No. 4,853,230 ("the '230 Patent") discussing the acid sensitivity of this class of compounds. When such compounds are exposed to the gastric environment, they can degrade within the stomach. This is not desirable. A common approach to protecting dosage forms is to use an enteric coating. However, enteric coatings are also somewhat acidic and thus can cause premature degradation of the highly acid sensitive benzimidazole proton pump inhibitors. Lovgren proposed using a separating layer to separate the active ingredient and alkaline material from the enteric coating. See Lovgren's U.S. Patent No. 4,786,505 ("the '505 Patent") and the 230 Patent. This approach is used in the Prilosec® dosage form of omeprazole currently marketed in the United States.

[1] On page 11, the top formula encompasses each of omeprazole, lanzoprazole, pantoprazole and rabeprazole when A is the pyridine ring with R_3, R_4 and R_5 selected from the substituents specified.

THE OBVIOUSNESS REJECTIONS

In the Office Action of July 27, 2007, The Examiner essentially repeated the prior obviousness rejections from the Office Action of November 14, 2006 and also repeated the same responses to the previously submitted Remarks except for the response set forth at the bottom of page 31 to the top of page 32 and at the top of page 34 of the July 2007 Office Action. Those responses will be addressed below. Otherwise, Applicant incorporates by reference the previously submitted traversals and arguments to the obviousness rejections as if set forth herein and supplements those traversals and arguments with the following additional remarks.

An important feature of the present invention is that it provides a stable pharmaceutical preparation even though no intermediate separating layer is added between the active containing region and the outer enteric coating of the dosage form. As previously indicated, a stable dosage form is achieved because of the formation of a substantially nonporous layer containing the active ingredient which results from the combination of process steps as recited in the claims.

None of the references cited by the Examiner teaches or suggests a process having the combination of *all* technical features of the claimed process.

The now claimed invention is new and unobvious in view of the cited art including Depui' 771 and '184 and WO9601624 ('624). These references describe:

i). proton pump inhibitors formulated into a core material, by compression (ex. **6** of '771 and ex. **6** of '184) or extrusion/spheronization (Ex. **9** and **14** of '771, Ex. **12, 15** and **17** of '184 and Ex **2** of '624) methods. In contrast, the pharmaceutical

preparation prepared in the present invention is a seed layered with active ingredient. And the now claimed process is conducted in a single Wurster-type fluid bed apparatus.

ii). Additionally, in the prior art, a seed (inert nucleus) layered with proton pump inhibitors is produced by powder layering (ex. **10** of '771, Ex. **13** of '184 and Ex **3** of '624). The now claimed process is directed to the preparation of a product consisting of a seed layered with proton pump inhibitors produced by solution/suspension layering. In addition, the claimed process is also different to the prior art methods since all the steps of the cited examples are not performed in a single fluid bed apparatus of Wurster-type.

The preparation of the new claimed process is not rendered obvious by any of Depui '77, Depui '184 or WO '624 alone or in combination.

Further, in contrast to the present invention, all above prior art examples, except example **11** of WO '624, clearly describes a seed having three layers (active, intermediate and enteric). However, in the present process there is no introduction of an intermediate layer. Example 11 of WO '624 is silent as to the presence or absence of an intermediate layer. However, the Molina Millan declaration filed in July 2006 showed that products according to Example 11 of WO '624 have such a poor stability so as to be effectively lacking in stability.

Also, none of the prior art examples describes a step of drying the active layer formed in step 1. Further, none of the prior art examples describes all three steps of active ingredient coating, drying and enteric polymer coating being performed as in the

now claimed process. Thus, the now claimed process is not shown or suggested by the prior art.

The Examiner's comment in page 28 that components of Depui's example 4 are present in a layer of the instant invention and thus stability is due to adding those prior art intermediate layer components to the active and enteric layer is not supported by the art. None of the excipients are known in the art as stabilizers.

In the prior art, the intermediate layer, comprised of film-forming polymers soluble in water or rapidly disintegrating in water with other excipients, when present gives stability when in the form of an actual physical material barrier positioned between the acid labile active ingredient region and the enteric coating. In the invention, HPMC (when present) acts as a binder agent in the layering of the inert seed whereas PEG and talc act as a plasticizer and a glidant respectively. None of them are known to impart chemical or acid stabilizing properties to this type of acid labile active ingredient. If the Examiner has any factual information to support her supposition, she is requested to comply with the provisions of 37 CFR 1.104(d)(2).

In the Office Action of July 2007, the Examiner called for at least six (6) additional showings including making pellets with different apparatuses. It is submitted that adequate tests have already been submitted including making pellets with different apparatus. Given the nature of the claimed subject matter, Applicant has already made an adequate and reasonable showing. An applicant should not be required to conduct testing on mere theoretical speculation. Evidence is required only in view of a *prima facie* case, not in view of theoretical speculations. No *prima facie* case has been made. Applicant's showings have adequately addressed lack of enablement of the prior art and

have also shown improved or unexpected results of the claimed invention over the prior art.

The first Molina Declaration (Molina, Bravo and Picornell) contained experiments wherein dosage forms were made using a centrifugal fluid-bed granulator (MP-1-Roto Processor centrifugal fluid-bed granulator from NIRO) which is an apparatus different from a Wurster type fluidized-bed coater. The centrifugal fluid-bed granulator is the type of apparatus that one of the skilled in the art would use in order to make a granulation process for agglomerating solid in particulate or powdered form, like the layering of an inert seed by the method of powder layering.

The object of that experiment was to reproduce section 1) of example 6 of EP 0 642 797 disclosing coating of inert seeds by the powder layering technique and to compare the resultant lansoprazole granules with those obtained from the process of the present invention which uses a solution/suspension layering method.

In the present process, all the recited steps including the drying are performed in the same apparatus providing a more simple and efficient process to obtain stable pharmaceutical dosage forms of benzimidazole anti-ulcer compounds which dosage forms are uniform, well shaped, having good friability and good stability without the addition of an intermediate separating layer.

The Examiner maintains that she has addressed the previously submitted declarations. Apparently, the Examiner does not fully appreciate Applicant's position. Applicant has submitted numerous declarations and has indicated that the cited prior art is lacking in numerous details to allow comparison. Therefore, Applicant has made comparisons to prior art, which because it provides details, it is in effect closer prior art

than that cited by the Examiner. To require Applicant to speculate as to what unspecified conditions may have been used in prior art examples which do not recite sufficient detail is unreasonable. Applicant has no way of knowing whether the examples were ever actually conducted or whether they are merely paper examples.It should be noted that the Examiner cites to only a portion of Example 4 of Depui '184. Clearly, Depui's composition and processing in that Example was intended to include a second active ingredient, additional processing and additional excipients to obtain the resulting dosage form. Further, the fact the prior art examples cited by the Examiner fail to provide information as to the stability of the resulting formulations renders comparisons to those examples not only speculative but uninformative.

Applicant has cited abundant authority including *In re Fouche*, 169 USPQ 429, 433, (CCPA 1971), which supports Applicant's position for the comparisons it has made. The *Fouche* decision is cited in the MPEP for this very proposition. See MPEP (8th Ed. Rev. 5) §716.02(b) (Direct and Indirect Comparative Tests Are Probative Of Non-Obviousness). The Examiner has not offered any reason why the submissions are not sufficient comparisons in view of *In re Fouche* and similar decisions or the fact that the cited prior art examples lack sufficient detail to allow a meaningful comparison even though Applicant has previously raised this concern. Otherwise, the PTO has not denied that the results obtained by the invention are unexpected. The Examiner's only challenge to the showing that the prior art lacks enablement is that the prior art makes "a pellet". Applicant claims a pharmaceutical preparation. No one of ordinary skill would consider a pellet which is stable for only an hour to be a useful, or stable "pharmaceutical preparation".

The Examiner has failed to establish on the record what degree (if any) of improvement would be expected from the process of the invention. Applicant has shown by citation to the Lovgren patents that no degree of improvement would be expected and that one would actually expect rapid degradation of a dosage form which was formed with an intermediate separating layer. Thus the fact that there is any improvement is unexpected. See *In re Soni*, 34 USPQ 2d 1684 (Fed. Cir. 1995).

In commenting on the Johansson Declaration, the Examiner appears to attempt to use a phrase of Johansson's statement against the declarant. However, this is in violation of the rule of *In re Ruff*, 118 USPQ 340, 346 (CCPA 1958). The declarant's comment was taken out of context. Clearly, the declarant, was commenting that the failure of the prior art formulation was no surprise based on not only the declarant's personal experience but also based on the teaching of the Lovgren patents.

Processes for providing dosage forms are patentable over the art. For instance, U.S. Patent No. 6,096,340 filed for in the United States in November of 1997 shows a process for obtaining dosage forms.

With respect to the Examiner's response to arguments starting at the bottom of page 31 continuing on to the top of page 32, the present claims do exclude a separating layer whereas the preparations disclosed in U.S. Patent 5,232,706 specifically recite a separating layer between the nucleus having the active ingredient and the enteric coating outer layer. Thus, the only point which this reference addresses is the identification of an alkaline compound.

The Kim reference is directed at a waxy omeprazole composition for rectal administration. Since the Kim reference represents that the area of administration is

alkaline in nature, it is clear that Kim's compositions do not involve or address, the problems faced with a pharmaceutical preparation for oral administration using pellets. Example 1 of the Kim reference is representative of the process therein and it is clear that Kim uses a simple manual or mechanical mixing process to form the compositions there of interest. Kim's composition shows a low bioavailability when orally administered. Thus, the Kim reference has no relevance to the patentability of the presently claimed process which is directed to producing an "oral pharmaceutical preparation".

Contrary to the Examiner's comment regarding that certain substances such as lysine were known to provide stability, this disclosure is only cumulative to the disclosure of the Lovgren patents which Applicant has repeatedly cited to the Examiner.

Contrary to the Examiner's comments on the top of page 34 of the Office Action, it is submitted that the there is no motivation to make the combination. The respective dosage forms are radically different in structure and use. One reference uses the intermediate separating layer to protect the active ingredient and does not suggest that in the absence of the intermediate layer that there would be any degree of protection to obtain a stable formulation dosage form. The composition of Kim is so radically different as to the dosage form and method of preparation from the subject matter of the present claims that one of ordinary skill in the art would not even look to Kim.

In view of the foregoing, reconsideration and allowance of the application with claims 16, 18 to 25, 30, 31, 33, 39 to 53 are earnestly solicited.

The Examiner is invited after reviewing the forgoing to telephone Applicant's undersigned attorney to advise of the status of the application or to resolve any remaining issues.

It is believed that no fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,

COHEN PONTANI LIEBERMAN & PAVANE LLP

By _____
Vincent M. Fazzari
Reg. No. 26,879
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

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